Chemistry of Heterocyclic Compounds, Vol. 42, No. 5, 2006

SYNTHESIS OF NEW 1H-1,2,4-TRIAZOLYLCOUMARINS AND THEIR ANTITUMOR AND ANTI-HIV ACTIVITIES

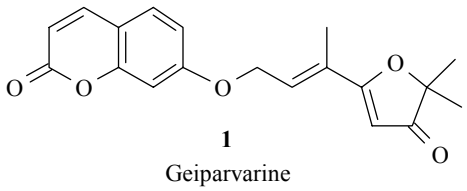
Y. A. Al-Soud[1], I. A. Al-Masoudi[2], B. Saeed[3], U. Beifuß[4], and N. A. Al-Masoudi[5]

A variety of 7-[(1,5-dialkyl-1H-1,2,4-triazolyl)methoxy(and methyl)]coumarins were synthesized from cycloaddition of 2-(2H-benzopyran-7-yloxy)acetonitrile and 2-(5-methoxy-4-methyl-2H-benzopyran-7-yloxy)acetonitrile, respectively, with various reactive cumulene $>C=\overset{+}{N}=N-$ *intermediates via spontaneous rearrangements. The anticancer (breast, lung, CNS cancers) and antiviral (HIV-1, HIV-2) properties of some compounds were investigated in vitro. 5-Methoxy-4-methyl-7-[(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[1,5-a]azepin-2-yl)methyl]coumarin showed some inhibition of HIV-1.*

Keywords: antitumor activity, antiviral activity, coumarin, 1,2,4-triazoles, cycloaddition.

Several coumarins constitute an important class of naturally occurring compounds with useful pharmacological activity [1-6] as antibacterial and antifungal agents [7, 8], and as serine protease inhibitors [9]. Geiparvarin **1**, a naturally occurring product bearing the coumarin residue, has been shown to possess a significant inhibitory activity against a variety of cell lines including sarcoma 180, *Lewis* lung carcinoma, P-388 lymphocytic leukaemia, and *Walker* 256 carcinosarcoma, [10, 11]; meanwhile some Geiparvarin analogues showed interesting biological activity [12]. Warfarin and some *bis*-hydroxycoumarins have been used as oral anticoagulants [13], β-adrenergic blocking agents [14], and vasorelaxants [15]. Recently, cloricromene, a coumarin derivative, was reported as a protector against collagen-induced arthritis in Lewis rats [16]. New furanocoumarin ethers of falcarindol, named *japonagelol*, have been prepared as novel antiproliferative agents [17].

On the other hand, it was reported that compounds having triazole moieties, such as vorozole, letrozole, and anastrozole, appeared to be effective aromatase inhibitors, which in turn prevented breast cancer [18-20].



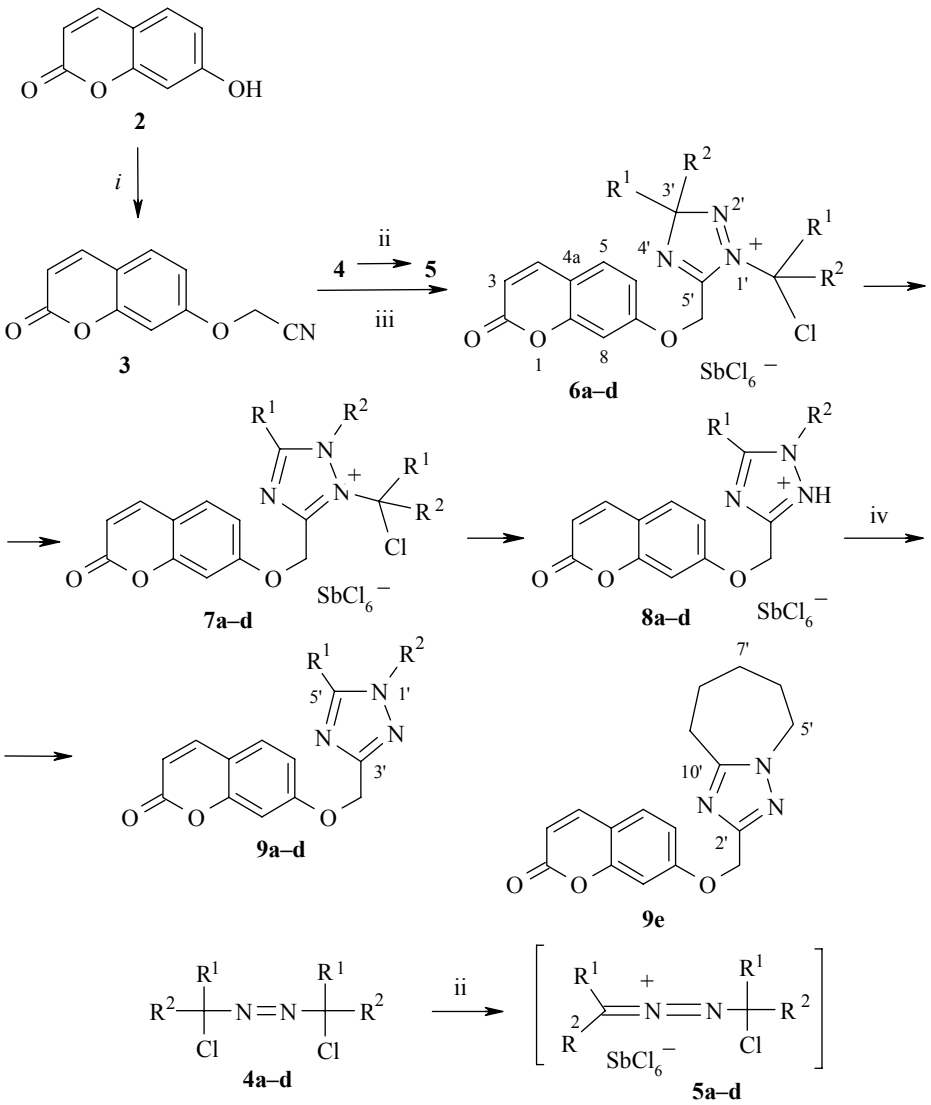
1
Geiparvarine

[1] Department of Chemistry, College of Science, University of Al al-Bayt, Al-Mafraq, Jordan; e-mail: alsoud@rocketmail.com. [2] College of Veterinary, University of Basrah, Basrah, Iraq; e-mail: faik1959@yahoo.com. [3] Department of Chemistry, College of Education, University of Basrah, Basrah, Iraq; e-mail: Bas_chem_dep@yahoo.com. [4] Fakultät für Chemie, Universität Hohenheim, Germany; e-mail: ubeifuss@uni-hohenheim.de. [5] Formerly Fachbereich Chemie, Universität Konstanz, Germany; e-mail: info@al-masoudi.de. Published in Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 669-678, May, 2006. Original article submitted February 20, 2006.

The biological importance of coumarin and 1,2,4-triazole prompted us to synthesize new 1,5-1H-1,2,4-triazole derivatives containing a coumarin backbone, which would be favorable in achieving some specificity of pharmacological action in view of the development of effective clinical anticancer and anti-HIV drugs.

Recently, we synthesized a variety of 1,5-dialkyl-1H-1,2,4-triazoles bearing different precursors such as C-nucleosides [21, 22], acyclic C-nucleosides [23], pyrimidines [24], N-alkylphthalimides [25], D-mannopentitol-1-yl-1,2,4-triazoles [26], 1H-indoles [27], quinolones [27], benzotriazoles [28], 3'-triazolothymidines [29], acetic acid alkylidene hydrazides [30], and 1,4-disubstituted piperazines [31-33].

Scheme 1



Reagents and conditions: i $ClCH_2CN$; ii $SbCl_5$, CH_2Cl_2, –60°C; iii CH_2Cl_2, –60°C to 23°C; iv $NaHCO_3$, NH_3, MeCN, 0°C, 2h

4-9 a $R^1 = R^2 = Me$; **b** $R^1 = Me$, $R^2 = Et$; **c** $R^1 = R^2 = Et$; **d** $R^1 = Me$, $R^2 = i\text{-}Pr$; **e** $R^1+R^2 = (CH_2)_5$

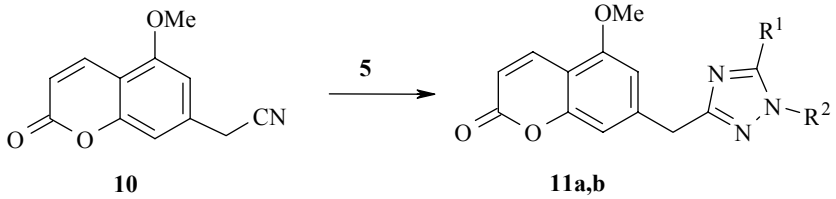
In the present study 2-(2H-benzopyran-7-yloxy)acetonitrile (**3**) was selected for the synthesis of new 1,2,4-triazole precursors. Nitrile **3** was prepared by treatment of 7-hydroxycoumarin (**2**) with 2-chloroacetonitrile in DMF containing K_2CO_3 [34]. The reactive intermediates **5** were obtained from the α,α'-dichloroazo compounds **4** [35] by treatment with $SbCl_5$ at -60°C. At approximately -30°C, the color changed from orange to brown, indicating that cumulenes **5a-e** underwent cycloaddition reactions with nitrile **3** to give inseparable 1,2,4-triazolium hexachloroantimonates **6a-e**. After increase in the temperature above -30°C, compounds **6a-e** rearranged spontaneously to the intermediates **7a-e** by migration of the alkyl group at C-3' *via* [1,2]-migration [36, 37] to N-5' accompanied by the elimination of the CMe_2Cl group at N-1' leading to the protonated 7-(1,5-dialkyl-1,2,4-triazol-3-ylmethyl)coumarin salts **8a-e**. *In situ* deprotonation of salts **8a-e** with aqueous $NaHCO_3$ and NH_3 solution gave the desired products **9a-e** in 72-85% yield.

Compounds **9a-e** were identified by the ^1H and ^{13}C NMR spectra, which are in agreement with those of coumarin analogues obtained previously [13, 33]. The CH_2 signal appeared as a singlet at the region of δ_H 5.01-5.10. The alkyl groups at N-1' and C-5' of the triazole ring were assigned. The signals of olefinic protons H-3 and H-4 appeared as two doublets at the regions of δ_H 6.19-6.22 and 7.60 ppm, respectively, with $J \sim 8.4$ Hz, while H-6 and H-8 appeared as multiplets in the range of δ_H 6.92-6.95 ppm. The ^{13}C NMR spectra of compounds **9a-e** contained similar resonance signals of the coumarin ring carbons C-2 – C-8a. The chemical shifts between δ_C 161.5-161.8 ppm were assigned to the carbonyl group of the benzopyran ring (C-2). The higher-field signals at δ 161.1 and 151.8-155.6 ppm were attributed to C-3' and C-5'. The resonance at δ_C 157.3-158.3 and ~102.0 ppm were assigned to the coumarin carbons C-8a, C-7, and C-8', respectively. CH_2 signals appeared between δ 63.8-64.0 ppm, whereas the alkyl groups at C-3' and C-5' resonated in the range of δ_C 43.1-11.8 ppm.

Compound **9e** was selected for homo- and heteronuclear NMR study. The gradient selected HMBC [38] spectrum allowed *via* $^2J_{C,H}$ and $^3J_{C,H}$ couplings the assignment of most of the carbon atoms. C-3' and C-7 at δ_C 161.1 and 158.3 were identified from their $^2J_{C,H}$ and $^3J_{C,H}$ correlations to CH_2 at δ_H 5.01, respectively, while C-5' at δ_C 151.8 was identified from its $^2J_{C,H}$ and $^3J_{C,H}$ correlations to CH_2-6' at δ_H 2.92, and CH_2-10' at δ_H 4.22, respectively. The NOESY spectrum of compound **9e** showed a $J_{H,H}$ correlation for the olefinic protons H-3 (δ_H 6.91 ppm) and H-4 (δ_H 7.60 ppm). Its mass spectra exhibited the correct molecular ion $[M]^+$ (311).

Our investigation into the synthesis of new potential coumarin derivatives bearing 1,2,4-triazoles has been extended starting with the coumarin backbone having a cyanomethyl group in position 7 as a comparative example for the cyanomethoxy derivative **3**. Thus, 2-(5-methoxy-4-methyl-2H-benzopyran-7-yloxy)acetonitrile (**10**) [39] was used as a starting material in our new route. Compounds **11a,b** were synthesized in 85 and 75% yield, respectively, from cycloaddition of nitrile **10** with cumulenes **5a,e** following the same procedure used for preparation of **9a-e** (Scheme 2). The structures of compounds **11a,b** were assigned from the ^1H, ^{13}C NMR, and mass spectra, which demonstrated a similar pattern to those of the oxygen analogues **9a,e**.

Scheme 2



10 **11a,b**

11 a $R^1 = R^2 = Me$, **b** $R^1+R^2 = (CH_2)_5$

Compounds **9a,c,e** and **11a,b** have been selected by the National Cancer Institute (NCI) for primary (one dose, 10^{-4} M) anticancer *in vitro* screening against three tumor cell lines: MCF7 (breast), NCI-H460 (lung) and SF-268 (CNS) [40] (Table 1). In the current protocol each cell line was inoculated and pre-incubated

on a microtiter plate, test agents were then added at a single concentration, and the culture incubated for 48 h. End point determination was made with sulforhodamine B, a protein-binding dye (alamar blue) [41]. The results for each test agent were reported as the percent of growth of the treated cells when compared to the untreated control cells. Compounds that reduced the growth of any cell line to approximately 32% or less were judged as having antitumor activity.

Regarding the results displayed in Table 1, these compounds were relatively inactive. The structure-activity relationship proved that substitution of the benzopyran-2-one ring with the 1,5-disubstituted 1,2,4-triazole residues would not affect the anticancer activity profile of these compounds in comparison with the corresponding analogue Geiparvarin **1**, which exhibited a significant activity against sarcoma 180, *Lewis* lung carcinoma, P-388 lymphocytic leukemia, and *Walker* 256 carcinosarcoma.

TABLE 1. *In Vitro* Primary Antitumor Activity Data for the Selected Compounds

Compound	Number assigned by NCI	Growth percentage of tumor cells* (human)		
		lung NCI-H460	breast MCF7	CNS SF-268
9a	726115	98	64	91
9c	726231	101	107	108
9e	726241	57	73	88

* Sample concentration 1×10^{-4} M. Results for each test agent are reported as the percentage growth of the treated cell compound to the untreated cells.

TABLE 2. *In Vitro* Anti-HIV-1 (IIIB) and HIV-2 (ROD) Activity of Triazolocoumarin Compounds

Com-pound	Strain	IC_{50}, μg/ml*	CC_{50}, μg/ml*[2]	SI*[3]
3	III_B	> 70.8	70.8	< 1.0
	ROD	> 67	67	< 1.0
9a	III_B	> 82.2	82.2	< 1.0
	ROD	88.3	88.3	< 1.0
9b	III_B	> 70.2	70.2	< 1.0
	ROD	> 66.3	66.3	< 1.0
9c	III_B	> 25	25	< 1.0
	ROD	> 25	25	< 1.0
9d	III_B	> 59.3	59.3	< 1.0
	ROD	> 60.8	60.8	< 1.0
9e	III_B	> 97.4	97.4	< 1.0
	ROD	> 113	113	< 1.0
11a	III_B	> 12.2	12	<1.0
	ROD	> 14.1	14.1	< 1.0
11b	III_B	> 0.17	0.17	< 1.0
	ROD	> 0.29	0.29	< 1.0

* Effective concentration of compound required to achieve 50% protection of MT-4 cells against the cytopathic effect of HIV.

*[2] Cytotoxic concentration of compound required to reduce the viability of Mock-infected MT-4 cells by 50%.

*[3] Selectivity index: ratio of CC_{50}/IC_{50}.

Compounds **3** and **9a-e** were evaluated for their anti-HIV activity in vitro using the III_B strain for HIV-1 and the ROD strain for HIV-2, and monitored by the inhibition of virus-induced cytopathy in MT-4 cells. The results are summarized in Table 2. None of the tested compounds was found to inhibit HIV-1 or HIV-2 replication in vitro at IC_{50} lower than the cytotoxic concentration (CC_{50}). Compound **11b** showed some encouraging result by inhibition of HIV-1 with IC_{50} value > 0.17 μM but with a CC_{50} of 0.17 μg/ml, resulting in a selectivity index of <1.0, after which no selectivity could be observed.

The structure-activity relationship suggested that compounds with the carbon-coumarin linkage manifested a higher HIV inhibitory activity than that of the corresponding analogues having the oxygen linkage. Such a result would lead us to modify our new target molecules by introduction of more potential groups with a carbon linkage.

EXPERIMENTAL

Melting points are uncorrected and measured on Büchi melting point apparatus B-545 (BÜCHI Labortechnik AG, Switzerland). Microanalytical data were performed by Vario, Elementar apparatus (Shimadzu). NMR spectra were recorded at 250 and 600 MHz (^1H) and at 150.91 MHz (^{13}C) spectrometers (Bruker, Germany) in $CDCl_3$ with TMS as an internal standard. The signal assignments for protons were identified by selective proton decoupling or by COSY spectra. Heteronuclear assignments were verified by ^1H-^{13}C COSY or HMQC experiments. Mass spectra were recorded on 70 eV EI and FAB MAT 8200 spectrometers (Finnigan MAT, USA), using nitrobenzyl alcohol or glycerol as matrices.

2-(2H-Benzopyran-7-yloxy)acetonitrile (3). A solution of coumarin **2** (1.50 g, 9.25 mmol) in DMF (30 ml) containing K_2CO_3 (1.90 g, 13.74 mmol) was stirred with 2-chloroacetonitrile (0.76 g, 10.0 mmol) for 4 h at 90°C. After cooling, the solution was evaporated to dryness and the residue was partitioned between $CHCl_3$ (3 × 30 ml) and water (40 ml). The combined organic extracts were dried (Na_2SO_4), filtered off, and evaporated to dryness. Recrystallization from EtOH gave nitrile **3** (1.52 g, 82%); mp 140-141°C (dec.). ^1H NMR, δ, ppm (*J*, Hz): 8.00 (1H, d, *J* = 9.5, H-4); 7.70 (1H, d, *J* = 8.6, H-5); 7.17 (1H, d, *J* = 2.3, H-8); 7.06 (1H, dd, *J* = 2.3, *J* = 8.6, H-6); 6.34 (1H, d, *J* = 9.5, H-3); 5.29 (2H, s, CH_2-1'). ^{13}C NMR, δ ppm: 160.1 (C-2), 159.2 (C-7), 155.1 (C-8a), 144.1 (C-4), 129.9 (C-5), 116.2 (CN), 113.9 (C-6), 113.8 (C-3), 112.6 (C-4a), 102.0 (C-8), 54.0 (CH_2). Mass spectrum, *m/z* (I_{rel}, %): 201 [M^+] (92). Found, %: C 65.43; H 3.42; N 6.82. $C_{11}H_7NO_3$. Calculated, %: C 65.67; H 3.51; N 6.96.

7-[(1,5-Dialkyl-1H-1,2,4-triazol-3-yl)methoxy]coumarin (9) (General Procedure). To a stirred, cooled (-60°C) solution of the required azo compound **4** (3.0 mmol) and nitrile **3** (0.32 g, 2.0 mmol) in dry CH_2Cl_2 (20 ml) was added dropwise a solution of $SbCl_5$ (3.0 mmol) in dry CH_2Cl_2 (30 ml). The solution was left to stand with stirring at -60°C for 1 h, then at 0°C for 1 h and finally at 23°C for 10 min, followed by addition of pentane (50 ml). The precipitated solid was dissolved in MeCN (40 ml), cooled to 0°C, followed by addition of $NaHCO_3$ aqueous solution (2.52 g, 30 mmol in 30 ml of water) and NH_3 solution (2 ml). The mixture was stirred at room temperature for 2 h, then the organic solvent was evaporated and the residue was extracted with $CHCl_3$ (3 × 20 ml). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness, the residue was recrystallized from EtOH or $CHCl_3$–pentane, and the oily compounds were purified on SiO_2 column.

7-[(1,5-Dimethyl-1H-1,2,4-triazol-3-yl)methoxy]coumarin (9a). From compound **4a** (0.54 g). Yield 0.45 g (83%); mp 188-189°C. ^1H NMR, δ, ppm (*J*, Hz): 7.60 (1H, d, *J* = 9.5, H-4); 7.33 (1H, d, *J* = 8.2, H-5); 6.92 (2H, m, H-6,8); 6.21 (1H, d, *J* = 9.5, H-3); 5.08 (2H, s, CH_2); 3.78 (3H, s, N–CH_3); 2.43 (3H, s, C-5-CH_3). ^{13}C NMR, δ, ppm: 161.5 (C-2), 161.1 (C-3'), 157.4 (C-7), 155.6 (C-8a), 153.3 (C-5'), 143.3 (C-4), 128.6 (C-5), 113.2 (C-6), 113.1 (C-3), 112.8 (C-4a), 101.9 (C-8), 63.8 (CH_2), 35.2 (N–CH_3), 11.8 (C-5-CH_3). Mass spectrum, *m/z* (I_{rel}, %): 271 [M^+] (80). Found, %: C 61.72; H 4.75; N 4.67. $C_{14}H_{13}N_3O_3$. Calculated, %: C 61.99; H 4.83; N 15.49.

7-[(1-Ethyl-5-methyl-1H-1,2,4-triazol-3-yl)methoxy]coumarin (9b). From compound **4b** (0.42 g). Yield 0.46 g (85%); mp 90-91°C. ^{1}H NMR, δ, ppm (*J*, Hz): 7.60 (1H, d, *J* = 9.5, H-4); 7.33 (1H, d, *J* = 8.4, H-5); 6.93 (2H, m, H-6,8); 6.21 (1H, d, *J* = 9.5, H-3); 5.09 (2H, s, CH_2); 4.08 (2H, q, *J* = 7.4, $C\underline{H}_2CH_3$); 2.44 (3H, s, N–CH_3); 1.42 (3H, t, *J* = 7.4, $CH_2C\underline{H}_3$). ^{13}C NMR, δ, ppm: 161.6 (C-2), 161.1 (C-3'), 157.4 (C-7), 155.6 (C-8a), 152.4 (C-5'), 143.3 (C-4), 128.6 (C-5), 113.2 (C-6), 113.1 (C-3), 112.8 (C-4a), 101.9 (C-8), 63.8 (CH_2), 43.4 ($\underline{C}H_2CH_3$), 14.8 ($CH_2\underline{C}H_3$), 11.8 (C-5-CH_3). Mass spectrum, *m/z* (I_{rel}, %): 285 [M^+] (80). Found, %: C 62.92; H 5.22; N 14.49. $C_{15}H_{15}N_3O_3$. Calculated, %: C 63.15; H 5.30; N 14.73.

7-[(1,5-Diethyl-1H-[1,2,4]-triazol-3-yl)methoxy]coumarin (9c). From compound **4c** (0.42 g). Yield 0.44 g (73%); mp 122-123°C. ^{1}H NMR, δ, ppm (*J*, Hz): 7.60 (1H, d, *J* = 9.5, H-4); 7.33 (1H, d, *J* = 8.3, H-5); 6.95 (2H, m, H-6,8); 6.21 (1H, d, *J* = 9.4, H-3); 5.10 (2H, s, CH_2); 4.08 (2H, q, *J* = 7.4, $C\underline{H}_2CH_3$); 2.73 (2H, q, C-5"-$C\underline{H}_2CH_3$); 1.43 and 1.34 (6H, 2t, $2CH_2C\underline{H}_3$). ^{13}C NMR, δ, ppm: 161.7 (C-2), 161.1 (C-3'), 157.4 (C-7), 157.1 (C-8a), 155.6 (C-5'), 143.3 (C-4), 128.6 (C-5), 113.2 (C-6), 113.1 (C-3), 112.7 (C-4a), 101.9 (C-8), 64.0 (CH_2), 43.1 (N–$\underline{C}H_2CH_3$), 19.3 (C-5-$CH_2\underline{C}H_3$), 15.1 (N–$CH_2\underline{C}H_3$), 11.8 (C-5-CH_2CH_3). Mass spectrum, *m/z* (I_{rel}, %): 299 [M^+] (83). Found, %: C 64.01; H 5.67; N 13.92. $C_{16}H_{17}N_3O_3$. Calculated, %: C 64.20; H 5.72; N 14.04.

7-[(1-Isopropyl-5-methyl-1H-1,2,4-triazol-3-yl)methoxy]coumarin (9d). From compound **4e** (0.42 g). Yield 0.43 g (72%); mp 94-96°C. ^{1}H NMR, δ, ppm (*J*, Hz): 7.61 (1H, d, *J* = 9.5, H-4); 7.33 (1H, d, *J* = 8.4, H-5); 6.94 (2H, m, H-6,8); 6.22 (1H, d, *J* = 9.5, H-3); 5.10 (2H, s, CH_2); 4.43 (1H, m, $CH(CH_3)_2$); 2.44 (3H, s, C-5'-CH_3); 1.48 and 1.46 (6H, 2s, $CH(C\underline{H}_3)_2$). ^{13}C NMR, δ, ppm: 161.8 (C-2), 161.1 (C-3'), 157.3 (C-7), 155.7 (C-8a), 151.8 (C-5'), 143.3 (C-4) 128.6 (C-5), 113.2 (C-6, C-3), 112.8 (C-4a), 102.0 (C-8), 64.0 (CH_2), 50.2 (N-1'-$\underline{C}H(CH_3)_2$), 22.2 (N-1'-$CH(\underline{C}H_3)_2$), 11.9 (C-5'-CH_3). Mass spectrum, *m/z* (I_{rel}, %): 299 [M^+] (70). Found, %: C 64.01; H 5.69; N 13.86. $C_{16}H_{17}N_3O_3$. Calculated, %: C 64.20; H 5.72; N 14.04.

7-[(6,7,8,9-Tetrahydro-5H-[1,2,4]-triazolo[1,5-*a*]azepin-2-yl)methoxy]coumarin (9e). From compound **4e** (0.42 g). Yield 0.51 g (81%); mp 159-160°C. ^{1}H NMR, δ, ppm (*J*, Hz): 7.60 (1H, d, *J* = 9.4, H-4); 7.32 (1H, s, *J* = 8.2, H-5); 6.93 (2H, m, H-6,8); 6.19 (1H, d, *J* = 10.7, H-3); 5.01 (2H, s, CH_2); 4.22 (2H, m, CH_2-5'); 2.92 (2H, m, CH_2-9'); 1.85 (2H, m, CH_2-6'); 1.80 (2H, m, CH_2-8'); 1.71 (2H, m, CH_2-7'). ^{13}C NMR, δ, ppm: 161.6 (C-2'), 161.1 (C-10'), 158.3 (C-7), 156.3 (C-8a), 143.3 (C-4), 128.6 (C-5), 113.1 (C-6, C-3), 112.8 (C-4a), 101.9 (C-8), 63.8 (CH_2), 51.2 (C-5'), 30.1 (CH_2-9'), 27.3 (CH_2-7'), 27.3 (CH_2-8'), 24.7 (CH_2-7'). Mass spectrum, *m/z* (I_{rel}, %): 311 [M^+] (72). Found, %: C 65.39; H 5.44; N 13.38. $C_{17}H_{17}N_3O_3$. Calculated, %: C 65.58; H 5.50; N 13.50.

5-Methoxy-4-methyl-7-[(1,5-dimethyl-1H-1,2,4-triazol-3-yl)methyl]coumarin (11a). From compounds **4a** (0.54 g) and **10** (0.46 g, 2.0 mmol). Yield 0.51 g (85%); mp 173-175°C. ^{1}H NMR, δ, ppm (*J*, Hz): 6.85 (1H, s, H-8); 6.70 (1H, s, H-6); 6.05 (1H, s, H-3); 5.05 (2H, s, CH_2); 3.89 (3H, s, OCH_3); 3.75 (3H, s, N–CH_3); 2.52 (3H, s, C-4-CH_3); 2.41 (3H, s, C-5'-CH_3). ^{13}C NMR, δ, ppm: 161.2 (C-2); 160.9 (C-3'); 157.9 (C-5); 152.8 (C-4, C-5'); 150.8 (C-8a), 136.2 (C-7), 112.2 (C-3, C-8), 109.3 (C-4a, C-6), 62.7 (CH_2), 56.1 (OCH_3), 35.2 (N–CH_3), 21.2 (C-4-CH_3), 11.7 (C-5-CH_3). Mass spectrum, *m/z* (I_{rel}, %): 299 [M^+] (90). Found, %: C 64.11; H 5.61; N 13.87. $C_{16}H_{17}N_3O_3$. Calculated, %: C 64.20; H 5.72; N 14.04.

7-[(6,7,8,9-Tetrahydro-5H-[1,2,4]-triazolo[1,5-*a*]azepin-2-yl)methyl]-5-methoxy-4-methylcoumarin (11b). From compounds **4e** (0.42 g) and **10** (0.51 g, 2.0 mmol). Yield 0.49 g (75%); mp 148-151°C. ^{1}H NMR, δ, ppm (*J*, Hz): 6.82 (1H, s, H-8); 6.68 (1H, s, H-6); 6.07 (1H, s, H-3); 5.01 (2H, s, CH_2); 4.22 (2H, m, CH_2-5'); 3.85 (3H, s, OCH_3); 2.92 (2H, m, CH_2-9'); 2.50 (3H, s, C-4-CH_3); 1.85 (2H, m, CH_2-6'); 1.80 (2H, m, CH_2-8'); 1.71 (2H, m, CH_2-7'). ^{13}C NMR, δ, ppm: 161.6 (C-2), 161.1 (C-2'), 158.1 (C-2', C-7), 152.5 (C-4), 112.0 (C-3, C-8), 109.1 (C-4a, C-6), 63.8 (CH_2), 56.0 (OCH_3), 51.2 (C-5'), 30.1 (CH_2-7') 27.3 (CH_2-9'), 27.3 (CH_2-8'), 24.7 (CH_2-7'), 21.1 (C-4-CH_3). Mass spectrum, *m/z* (I_{rel}, %): 339 [M^+] (91). Found, %: C 67.01; H 6.17; N 12.16. $C_{19}H_{21}N_3O_3$. Calculated, %: C 67.24; H 6.24; N 12.38.

We thank Dr. E. Sauville (Drugs Synthesis & Chemistry Branch, National Cancer Institute, NCI, Maryland, USA) for the antitumour screening and Professor E. De Clercq of Rega Institue of Medical Research, Katholieke Universiteit, Leuven, Belgium, for the anti-HIV screening.

REFERENCES

1. C. Ito, M. Chiliro, S. Katsuno, M. Omura, H. Tokuda, H. Nishino, and H. Furukawa, *J. Nat. Prod.*, **63**, 1218 (2000).
2. A. Z. Abyshev, G. I. D'Yachuk, E. V. Semenov, and M. P. Pukhov, *Pharm. Chem. J.*, **27**, 66 (1993).
3. C. A. Kontogiorgis and D. J. Hadjipavlou, *Bioorg. Med. Chem. Lett.*, **14**, 611 (2004).
4. A. Z. Abyshev, A. T. Alekseev, V. G. Platonov, and I. A. Byrkin, *Pharm. Chem. J.*, **30**, 441 (1996).
5. C. Teran, L. Santana, E. Uriarte, Y. Fall, L. Lena, and B.-R. Tolf, *Bioorg. Med. Chem*. *Lett.*, **8**, 3570 (1998).
6. T.-C Wang, Y.-L. Chen, C.-C. Cherng, S.-S. Liou, Y.-L. Chang, and C.-M. Teng, *Helv. Chim. Acta*, **79**, 1620 (1996).
7. A. M. El-Syed, A.-B. A. G. Ghattas, M. T. El-Wassimy, and O. A. Abd Allah, *Farmaco*, **54**, 56 (1999), references therein.
8. M. E. Kuehne, US Pat. 3,142,676; *Chem. Abstr.*, **61**, 8319 (1964).
9. L. Pochet, R. Frederic, and B. Masereel, *Curr. Pharm. Design*, **10**, 3781 (2004).
10. K. Padmawinata, *Acta Pharm*., **4**, 1 (1973); *Chem. Abstr*., **79**, 758970 (1973).
11. J. P. Jerris and A. B. Smith, *J. Org. Chem.*, **46**, 577 (1981).
12. Y.-L. Chen, T.-C. Wang, C.-C. Tzeng, and N.-C. Chang, *Helv. Chim. Acta*, **82**, 191 (1999).
13. J. Hirsh, V. Fuster, J. Ansell, and L. Halperin, *J. Am. College Cardiology*, **41**, 1633 (2003).
14. Y. Sato, Y. Kobayashi, T. Nagasaki, T. Oshima, S. Kumakura, K. Nakayama, H. Koike, and H. Takagi, *Chem. Pharm. Bull.*, **20**, 905 (1972).
15. Y.-L. Chen, T.-C. Wang, N.-C. Chang, Y.-L. Chang, C.-M. Teng, and C.-C. Tzeng, *Chem. Pharm. Bull.*, **46**, 962 (1998).
16. S. Cuzzocrea, E. Mazzon, C. Bevilacqua, G. Costantino, D. Britti, G. Mazzullo, A. De Sarro, and A. P. Caputi, *Br. J. Pharmcacol.*, **131**, 1399 (2000).
17. K. Furumi, T. Fujioka, H. Fujii**,** H. Okab, Y. Nakano, H. Matsunaga, M. Katano, M. Mori, and K. Mihashi, *Bioorg. Med Chem. Lett.*, **8**, 93 (1998).
18. P. E. Goss and K. Strasser-Weippl, *Best Pract. Res. Clin. End. Met.*, **18**, 113 (2004).
19. R. J. Santen, *Steroids*, **68**, 559 (2003).
20. M. Clemons, R. E. Coleman, and S. Verma, *Cancer Treat. Rev*., **30**, 325 (2004).
21. N. A. Al-Masoudi, N. A. Hassan, Y. A. Al-Soud, P. Schmidt, A. E-D M. Gaafer, M. Weng, S. Marino, A. Schoch, A. Amer, and J. C. Jochims, *J. Chem. Soc*., *Perkin Trans. 1*, 947 (1998).
22. Y. A. Al-Soud, W. A. Al-Masoudi, R. A. El-Halawa, and N. A. Al-Masoudi, *Nucleosides*, *Nucleotides*, **18**, 1985 (1999).
23. N. A. Al-Masoudi and Y. A. Al-Soud, A. Geyer, *Tetrahedron*, **55**, 751 (1999).
24. Y. A. Al-Soud and N. A. Al-Masoudi, *Pharm. Pharm. Med. Chem.*, **332**, 143 (1999).
25. Y. A. Al-Soud and N. A. Al-Masoudi, *Pharmazie*, **56**, 372 (2001).
26. N. A. Al-Masoudi, Y. A. Al-Soud, and I. Lagoja, *Carbohydr. Res.*, **318**, 67 (1999).
27. Y. A. Al-Soud, and N. A. Al-Masoudi, *Org. Prep. Proced. Int.*, **49**, 658 (2002).
28. Y. A. Al-Soud, N. A. Al-Masoudi, and A. R. S. El-Ferawnah, *Bioorg. Med. Chem.*, **11**, 1701 (2003).
29. Y. A. Al-Soud and N. A. Al-Masoudi, *Heteroatom Chem.*, **14**, 298 (2003).
30. Y. A. Al-Soud, M. N. Al-Dweri, and N. A. Al-Masoudi, *Farmaco*, **59**, 775 (2004).

31. Y. A. Al-Soud and N. A. Al-Masoudi, *Farmaco*, **59**, 41 (2004).
32. Y. A. Al-Soud, M. N. A. Qalalweh, H. H. Al-Sa'doni, and N. A. Al-Masoudi; *Heteroatom Chem.*, **16**, 28 (2005).
33. N. A. Al-Masoudi, I. A. Al-Masoudi, I. A. I. Ali, Y. A. Al-Soud, B. Saeed, and P. La Colla, *Acta Pharm*., **56**, 175 (2006).
34. A. Balbi, E. Sottofattori, T. Grandi, M. Mazzei, D. S. Pyshnyi, S. C. Lokhov, and A. V. Lebede, *Bioorg. Med. Chem.*, **5**, 1903 (1997).
35. Y. A. Al-Soud, W. Wirschum, N. A. Hassan, G. M. Maier, and J. C. Jochims, *Synthesis*, 721 (1998); references therein.
36. Q. Wang, J. C. Jochims, St. Köhlbrandt, L. Dahlenburg, M. Al-Talib, A. Hamed, and A. E. Ismail, *Synthesis*, 710 (1992).
37. Q. Wang, M. Al-Talib, and J. C. Jochims, *Chem. Ber.*, **127**, 541 (1994).
38. W. Willker, D. Leibfritz, R. Kerssebaum, and W. Bermel, *Magn. Res. Chem*., **31**, 287 (1993).
39. F. Eiden and P. Meins, *Pharmazie*, **305**, 124 (1972).
30. A. Monks, D. Scuiero, P. Skehan, R. Shoemaker, K. Paull, D. Vistica, C. Hose, J. Langley, P. Cronise, A. Vaigro-Wolff, M. Gray-Goodrich, H. Campbell, J. Mayo, and M. Boyd, *J. Natl. Cancer Inst.*, **83**, 757 (1991).
41. G. D. Gray and E. Wickstrom, *Biotechniques*, **21**, 780 (1996).